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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,083	08/22/2001	Yixin Wang	P 280651 A0000364	7368
909	7590	12/01/2004	EXAMINER LY, CHEYNE D	
PILLSBURY WINTHROP, LLP P.O. BOX 10500 MCLEAN, VA 22102			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,083	WANG ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 August 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-32 is/are pending in the application.
- 4a) Of the above claim(s) 19-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-18 and 28-32 is/are rejected.
- 7) ☒ Claim(s) 12 is/are objected to.
- 8) ☒ Claim(s) 12-32 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/26/2004</u> | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Applicants' arguments filed August 26, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.
2. The addition of claims 28-32 has been acknowledged.
3. The amendment to the specification has been entered.
4. Claims 12-18 and 28-32 are examined on the merits.

RESTRICTION REQUIREMENT

RESPONSE TO ARGUMENTS

5. Applicant traverses the withdrawal of claims 19-27 on the basis that "claims 19-27 simply further define, in a different manner, the invention of claims 12-17." Applicant's argument has been fully considered and found to be unpersuasive. Because the inventions as recited by claims 12-18, and 19-27, respectively, are distinct for the reasons given in the previous Office Action, mailed May 18, 2004, and the lack overlapping searches required for the respective distinct inventions support that the restriction for examination purposes as indicated as proper.
6. Further, Applicant argues that "[t]he first step of the method of claim 19 corresponds to the next-to-last step of claim 12 and to the subject matter of claim 15." Applicant's argument has been fully considered and found to be unpersuasive. It is noted that claim 12 ends on line 16 as denoted by the period. Claim 19 does not recite any limitations that could reasonably

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construed as the "the next-to-last step of claim 12." The limitations recited in claims 15 and 19 are respectively distinct, and the lack overlapping searches required for the respectively distinct inventions supports that the restriction for examination purposes as indicated as proper.

7. The requirement is still deemed proper and is therefore made FINAL.

OBJECTIONS

8. Claim 12 is objected to because said claim contains a period in line 2, after the term "comprising" wherein claim 12 does not end at line two. Appropriate correction is required.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 12-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. NEW MATTER REJECTION.

11. This rejection is maintained with respect to claims 14 and 18, as recited in the previous office action mailed May 18, 2004.

12. The instant rejection directed to claim 12 and dependent claims 13-18 has been necessitated by claim amendments.

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13. Claim 12 recites the limitation of "preparing a test sample comprising labeled nucleic acid molecules having sequences that provide a match to mRNA sequences in the tissue sample" in lines 6-7 which has not been found in the pointed to disclosure. It is noted that page 5, [0021], discloses "twenty pairs of perfect match and mismatch oligonucleotide probes" which is different from the limitation of "a match to mRNA sequences in the tissue sample". Page 8, [0033], discloses "each target may be prepared from a set of cell dishes or tissue samples by isolation of RNA over a course of time" which is different from the limitation of "a match to mRNA sequences in the tissue sample". Further, the disclosure of Sample Preparation and Hybridization Phase in paragraphs [0038] to [0040] is different from the amended limitation recited in lines 6-7.

14. Claim 12 recites the limitation of "incubating...with an array of oligonucleotide probes having sequences of alternative splicing regions of mRNAs expressed in the tissue sample,...occurs" in lines 8-11, which has not been found in the instant specification. Further, the disclosure of Sample Preparation and Hybridization Phase in paragraphs [0038] to [0040] is different from the amended limitation recited in lines 8-11.

15. Specific to claim 14, lines 5-7, the removal of lines 5-7 by claim amendment adds new matter to said claim. The instant specification does not have written description basis as originally filed for amended claim 14 due to the removal of lines 5-7. For example, the broadened claim 14 no longer requires the phenol chloroform extraction and ethanol precipitation step which is a required step for the claimed invention as disclosed by the instant specification (page 9, [0038]). Further, Figure 3 discloses the requirement of the step of "purify and quantify cDNA" which is no longer required by claim 14. The limited

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disclosure of the instant specification as originally filed does not provide written description support to the amended claim 14.

16. Specific to claim 18, line 2, the recitation "a computer to perform one or more steps of the method of claim 12" is considered to be new matter because the written description basis as filed for a method for performing one step or only two steps of claim 12 has not been found in the instant specification. It is noted that the instant specification provides support of a system and method comprising performing a plurality of steps (greater than two) for predicting alternative splicing transcripts (Figures 2-6). However, support for a computer to perform one or more tasks (only two) of the method of claim 12 has not been found in the instant specification as originally filed.

RESPONSE TO ARGUMENTS

17. Applicant argues that "phenol chloroform extraction and ethanol precipitation was one of several commonly used techniques for preparing nucleic acids prior to at hybridization assay." Applicant further argues that the specification "does not suggest or imply that purification of DNA of DNA using phenol chloroform extraction and ethanol precipitation is a critical step of the invention." Applicant's argument has been fully considered and found to be unpersuasive. It is noted that the instant specification discloses the required step of "purify and quantify cDNA" which may be performed by phenol chloroform extraction and ethanol precipitation (page 9, [0039], and Figure 3). However, claim 14 does not recite the "purify and quantify cDNA" step. The disclosure for the step of "purify and quantify cDNA" as cited in the specification has been reasonably construed as a critical limitation of the claimed invention. The claimed invention not requiring the "purify and quantify cDNA" step

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has not been found in the instant specification. Therefore, the limited disclosure of the instant specification as originally filed does not provide written description support to the amended claim 14.

18. Applicant's argument that "one of skill in the art would not reasonably consider that computer control of all of the steps of claim 12 is a required feature of the claimed invention" has been fully considered and found to be unpersuasive. It is noted that the instant specification provides support for a system and method comprising performing a specified set of computer controlled steps for predicting alternative splicing transcripts (Figures 2-6). However, support for the broader limitation of a computer to perform one or more steps as embodied in claim 12 has not been found in the instant specification as originally filed.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

21. This rejection is maintained with respect to claim 16, as recited in the previous office action mailed May 18, 2004.

RESPONSE TO ARGUMENT

22. Applicant's argument by pointed to support, page 11, has been fully considered and found to be unpersuasive. It is noted that paragraph [0044] discloses "uninformative probes" and "non-informative probe threshold (NIPT)" which Applicant argues as being "used

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interchangeably.” However, the pointed to support does not resolve the vague and indefinite issue of the limitation of “uninformative probes” limitation. Is the limitation of “uninformative probes” being directed to thresholds as in the phrase “non-informative probe threshold”? Or the limitation of “uninformative probes” is directed to nucleic acid sequences?

BASIS FOR REJECTION

23. Specific to claim 16, lines 5-6, the phrase “uninformative probes” causes the claim to be vague and indefinite because it is unclear what criteria are being used to consider that a probe is “uninformative” (lack of signal or false signal due to non-specific hybridization).

Clarification of the metes and bounds of the instant claim is required.

CLAIM REJECTIONS - 35 USC § 101

24. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

25. Claims 28-32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

26. The instant rejection has been necessitated by claim amendments.

27. Claims 28-32 are rejected because said claims are directed to a computer readable medium comprising steps for processing data without any physical alteration step, which is considered to be non-statutory subject matter. “For example, a computer process that simply calculates a mathematical algorithm that models noise is nonstatutory. However, a claimed process for digitally filtering noise employing the mathematical algorithm is statutory.”

(MPEP § 2106 (IV)(B)(2) (b), part ii). Similar to the nonstatutory example above, the instant

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invention comprises algorithmic steps for processing data without any physical alteration resulted from said processing steps. Further, the instant invention is directed to a computer readable medium wherein the data processing activity does not cause any physical transformation outside of said computer readable medium as a result of said activity.

Therefore, "such activity is not determinative of whether the process is statutory because such transformation alone does not distinguish a statutory computer process from a nonstatutory computer process" (MPEP § 2106 (IV)(B)(2) (b), part ii).

28. It is noted that the claimed invention as recited by claim 18 is directed to statutory subject matter because said claim embodies physical transforming limitations from claim 12.

CLAIM REJECTIONS - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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31. Claims 12-18 and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emmert-Buck et al. (2000) taken with Schena et al. (1996).

32. This rejection is maintained with respect to claims 12-18, as recited in the previous office action mailed May 18, 2004. The instant rejection has been extended to claims 28-32 as necessitated by claims amendments.

RESPONSE TO ARGUMENT

33. Applicant argues that Emmert-Buck et al. and Schena et al. do not describe or suggest “the claimed invention...which enables one to predict if a gene is expressed as alternative splice variants in two or more different tissue types.” Applicant argues that the “present invention obviates the need to perform DNA sequencing to determine if a differentially expressed transcript of interest is a splice variants as described by Emmert-Buck et al.” via the citation of Chuaqui et al. and Cole et al. Applicant’s arguments have been fully considered and found to be unpersuasive because the argued limitations are not required by the claimed invention as recited by claims 12-18 and 28-32. Therefore, the citation of said argued limitations is not required to render the claimed invention as being obvious over the prior art of Emmert-Buck et al. in view of Schena et al.

BASIS OF PRIOR ART REJECTION

34. Emmert-Buck et al. discloses the use of molecular profiling to produce insights and predictions of function of sequences (page 1109-1110, Molecular Profiling §). The method of Emmert-Buck et al. uses differential gene expression (microarray) for generating new insights for predicting novel splice variance of PB39 mRNA transcript (page 1112, column 1, lines 36-58), as instant claim 12, lines 1-2 and 6-7.

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35. Emmert-Buck et al. discloses a second splice variant prediction, which is the protein product of the alternative splice form of said transcript (page 1112, column 1, last line, to column 2, line 2), as in instant claim 13.

36. However, Emmert-Buck et al. does not disclose the limitations to claim 12, lines 3-5, and claims 14-18.

37. Emmert-Buck et al. cites Schena et al. (Citation Number 8) as an author of technologies capable of global gene expression measurements (page 1109, column 2, lines 11-13).

38. Schena et al. discloses a well-known in the art technique for test sample preparation wherein mRNA is extracted from tissues, purified and quantified; and hybridization and scanning are performed for data processing (Schena et al., page 10614, columns 1-2), as in claim 12, lines 3-5, and claim 14.

39. Schena et al. discloses hybridization signals were observed to be greater than 95% (threshold) of the human cDNA array elements, but not for any of the negative controls (Schena et al., page 10615, column 2, lines 6-8 and Figure 1). Each of the tissue samples was normalized to the control (filter) to generate an expression profile for each of the 1046 clones present on the array (Schena et al., page 10617, column 2, lines 6-10). Database searches revealed perfect matches (threshold) for five of the six sequences (Schena et al., page 10617, column 1, lines 20-23). Table 1 contains data as directed to the normalized difference of the two ratios wherein said ratios are greater than half the average ratio. The accession number reflects the highest score for the proximal and distal sequence traces (prioritize) (Schena et al., page 10616, Figure 2 and Table 1), as in instant claims 15 and 17.

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40. Table 1 contains data as directed to the normalized difference of the two ratios wherein said ratios are greater than half the average ratio (Schena et al., page 10616, Figure 2 and Table 1). Figure 3 illustrates the tissue specific gene expression values for 15 genes across said tissues. Tissue samples were normalized to the control to generate an expression profile for each of the 1046 clones. Detectable (threshold) expression was observed for all 15 genes in the four specific tissues types examined (across) and the relative expression is determined among the tissues (page 10617, column 2, lines 6-20). The method of Schena et al. comprises determining the final fluorescence ratios by taking the average of the ratios (relative signal strength) of two independent hybridizations (page 10614, column 2, Hybridization and Scanning), as in instant claim 16.

41. The arrays were scanned using a fluorescence laser scanning device (page 10614, column 2, Hybridization and Scanning) and pseudocolor representations of fluorescent images (preprocessing hybridization data of claim 12 (at least one task of claim 12)) were made with National Institutes of Health IMAGE software (computer readable medium with instructions) (Schena et al., page 10615, column 1, Computer Graphics and Informatics §), as in instant claims 18 and 28-32.

42. Emmert-Buck et al. disclose improvements in biomedical research techniques such as molecular profiling with the potential to increase dramatically our understanding of how cellular mechanisms response to the environment (page 1109, column 2, lines 2-16).

Further, Emmert-Buck et al. cites Schena et al. (Citation Number 8) as an author of technologies capable of global gene expression measurements (page 1109, column 2, lines 11-13) wherein said data is used produce insights and predictions as directed to diseases

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(page 1109, column 2, Molecular Profiling §). Therefore, the improvement of Emmert-Buck et al. is directly applicable to the method of analyzing cDNA expression data generated from a microarray as taught by Schena et al.

43. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the improvements disclosed by Emmert-Buck et al. and practice the method of predicting alternate splicing transcripts by analyzing cDNA expression data generated by the method of Schena et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to practice the method of predicting alternate splicing transcripts by analyzing cDNA expression data as taught by Emmert-Buck et al. and Schena et al.

CONCLUSION

44. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

45. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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46. This application contains claims 19-27 drawn to an invention independent or distinct from the invention originally claimed, filed February 02, 2004. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

47. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

48. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

49. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.


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50. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

51. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

C. Dune Ly

11/23/04


MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
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